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Synthesis of Meiosis-Activating Sterols Containing Fluorine

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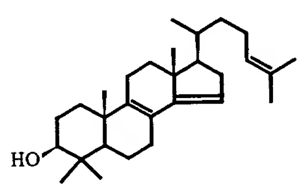
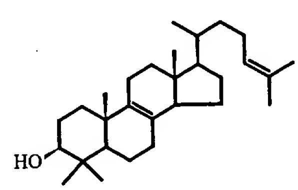
It is documented that specific types of sterol play a major role in the resumption of meiosis in oocytes from mice *in vitro*. 4,4-Dimethyl-5α-cholesta-8,14,24-trien-3β-ol (FF-MAS) isolated from human follicular fluid and 4,4-dimethyl-5α-cholesta-8,24-dien-3β-ol (T-MAS) isolated from bull testicular tissue, have been shown to activate (promote) meiosis *in vitro*. In order to evaluate the biological activity and stability of such compounds, new demethylsterol derivatives have been synthesised. Using diethylaminosulfur trifluoride (DAST) it was possible to synthesise selected Δ^8, Δ^{14} sterols with mono and difluoro substitution at C3.

It is documented[1] that specific types of sterol play a major role in the resumption of meiosis in oocytes from mice *in vitro*. These include follicular fluid-MAS (FF-MAS, 4,4-dimethyl-5α-cholesta-8,14,24-trien-3β-ol) obtained from women undergoing treatment for infertility by *in vitro* fertilization, testicular-MAS (T-MAS, 4,4-dimethyl-5α-cholesta-8,24-dien-3β-ol) obtained from bull testicular tissue, and two synthetic sterols 4,4-dimethyl-5α-cholesta-8,14-dien-3β-ol and 4,4-dimethyl-5α-cholest-8-en-3β-ol[1] (Fig. 1). These sterols have been known for some time but their importance in inducing meiosis is novel. They are known as intermediates in the biosynthesis of cholesterol from lanosterol. During this biosynthesis the two methyl groups in the 4-position are removed, and the double bond in the 24-position is reduced.[2] Therefore 4,4-demethyl sterols with a saturated side chain are of interest as potential meiosis-inducing agents.

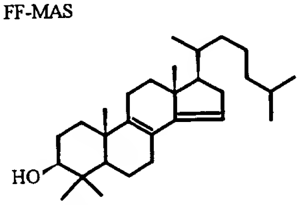
Introduction of fluorine into biologically active compounds is a well established approach to altering potency and metabolic stability.[3] Examples thereof are 5-fluorouracil,[4] fluorooestrogen analogues[5] and 4-fluoro-4-en-3-keto steroids[6] known to have novel pharmacological effects. As part of an approach to identify compounds which influence meiosis we chose to investigate the effect of substituting the 3-hydroxy group of sterols with one or two fluorine atoms. The introduced fluorine substituent might, like a hydroxy group, act as a hydrogen bond



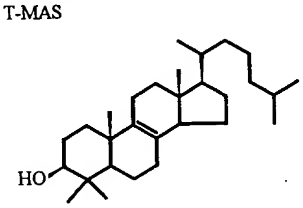
4,4-Dimethyl-cholest-8,14,24-trien-3 β-ol
FF-MAS



4,4-Dimethyl-cholest-8,24-dien-3 β-ol
T-MAS



4,4-Dimethyl-cholest-8,14-dien-3 β-ol



4,4-Dimethyl-cholest-8-en-3 β-ol

Fig. 1. Known sterols that promote the meiosis of oocytes *in vitro*.

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acceptor and therefore retain potency with increased biostability.

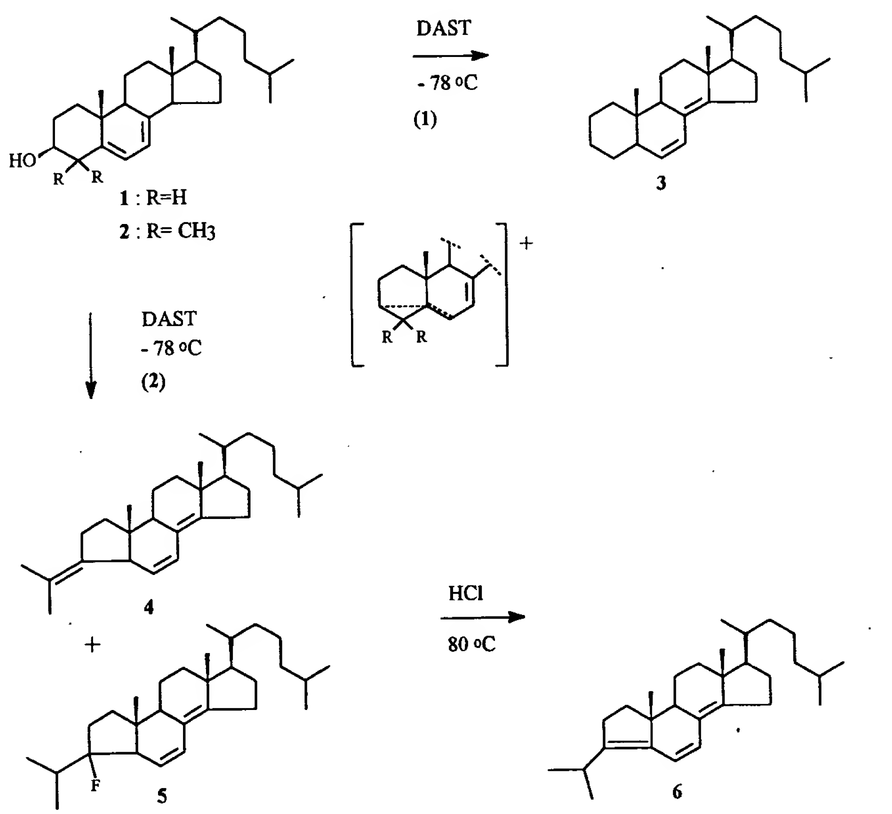
Diethylaminosulfur trifluoride (DAST)[7] has been used for replacement of hydroxy groups with fluoride in steroids[8] and 3β-hydroxysterols,[9] and to convert carbonyl compounds into *gem*-difluoro compounds in 5α-androstane[10] and hydroxy-vitamin D_3.[11] With DAST, alcohols are normally fluorinated with overall inversion of configuration pointing to an S_N2 reaction. However, treatment of cholesterol with DAST results in fluorination with retention of configuration and can be explained by neighbouring group participation which proceeds via a cyclopropyl–homoallyl carbocation.[7]

Results and discussion

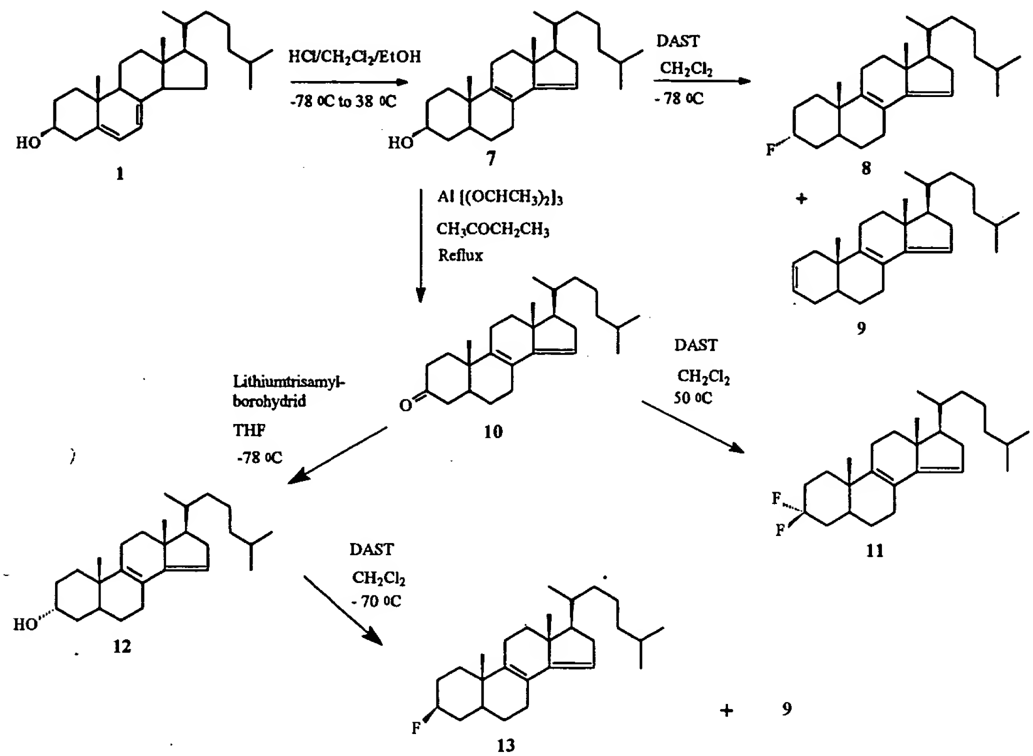
7-Dehydrocholesterol (**1**) and 4,4-dimethylcholesta-5,7-dien-3β-ol (**2**) were used as starting materials, to gain access to the two 3β-fluoro derivatives. Treatment of **1** with DAST under acidic, alkaline or neutral conditions all resulted in reduction of the hydroxy group and isomerisation of the two double bonds to the Δ^6, $\Delta^{8(14)}$-position (**3**). From the NMR spectrum it could be seen that the product, during work-up, was reduced to give **3** and we can give no plausible explanation for this. Treatment of **2** with DAST resulted in rearrangement of the A-ring to give **4** and **5** as the only isolable products as previously described for other analogues[12] (Scheme 1). Attempts to isomerise the double bonds of **5** with HCl gave only the defluorinated **6**.

It became clear that we had to fluorinate the end product. Also the two double bonds in **1** had to be isomerised before substitution with fluorine. Using a modified procedure **1** was treated with HCl to shift the two double bonds into the 8,14-position (Scheme 2). The reaction was carried out in CH_2Cl_2 instead of CCl_4 as previously described.[13] The reaction mixture was treated with HCl at −70 °C and then allowed to warm to room temperature (20 °C), whereupon the mixture was refluxed for 1 h. By this procedure it was possible to obtain pure 5α-cholesta-8,14-dien-3β-ol (**7**) with no 5β-isomer as determined by ^1H, ^{13}C NMR: E-COSY, DEPT, COSYS, HSQC and HMBC.

Alcohol **7** was treated with DAST to obtain a mixture of the 3α-fluoro compound (**8**) and the dehydrated compound (**9**). Ketone **10**, obtained by Oppenauer oxidation of **7**, was treated with lithium trisiamylborohydride (LS-Selectride®) to give the 3α-hydroxy compound (**12**).[14] **12** was reacted with DAST to give a mixture of the 3β-fluoro compound (**13**) and **9**. **10** was, in addition, treated with DAST to give the *gem*-difluoro compound (**11**). The fluorinated sterols (**8, 11** and **13**), which have not been described previously, were characterised by ^1H, ^{13}C and ^{19}F NMR and mass spectroscopy and microanalysis. The biological data will be published later.



Scheme 1. Approach to the synthesis of 3β-fluoro sterol derivatives.



Scheme 2. The synthesis of selected sterols containing fluorine.

Experimental

All reagents were purchased from Aldrich or Merck and were used without further purification. Melting points were determined on a DuPont 910 differential scanning calorimeter (DSC) or an Electrothermal IA9100 digital melting point apparatus and are uncorrected. High-resolution EI mass spectra were recorded on an HP MSD 5970 at 70 eV. The ^1H and ^{13}C NMR (E-COSY, DEPT, COSYS, HSQC and HMBC) spectra were recorded on a Bruker BZH 400/52 (400 MHz) instrument for samples in $CDCl_3$ with Me_4Si as an internal standard. ^{19}F NMR spectra were recorded on a Bruker AC 250 (250 MHz) for samples in $CDCl_3$ using $CFCl_3$ as an internal standard. Microanalyses were carried out in doublets on a Perkin–Elmer 240B elemental analyser. HPLC was carried out on a Merck Hitachi RPC Zorbax 50DS L-4000 UV detector (flow 0.5 ml min^{-1}, 230 nm, eluent 4‰ Pr^iOH in heptane, column: NPC Diol).

5α-Cholesta-6,8(14)-diene (**3**). Compound **1** was treated with DAST under different conditions. DAST (0.12 g, 0.68 mmol) in CH_2Cl_2 (2 ml) was added to a solution of **1** (0.1 g, 0.26 mmol) in CH_2Cl_2 (5 ml) and 0.5 ml HCl at -78 °C. After 30 min, the reaction was treated with H_2O (1 ml) and CH_2Cl_2 (5 ml). The organic layer was washed with 5 ml 5% $NaHCO_3$ and 5 ml H_2O. The organic layer was dried over $MgSO_4$ and evaporated to dryness, giving an oily residue (**3**) as the only product: ^1H NMR ($CDCl_3$): δ 6.16 (d, 1 H, $J_{6,7}$ 10 Hz, H7), 5.2 (d, 1 H, $J_{6,7}$ 10 Hz, H6), 2.5–0.4 (m, 42 H). ^{13}C NMR ($CDCl_3$): δ 147.20 (C14), 130.56 (C6), 124.60 (C8), 124.07 (C7). ^1H and ^{13}C NMR data correspond to earlier findings.[13] HCl was replaced by either heptane (2 ml) or pyridine (0.5 ml), which gave only **3** in all cases. The yields from the different conditions were between 54% and 100%.

4-Nor-3-isopropylcholesta-3,6,8(14)-triene (**4**) *and 4-nor-3-fluoro-3-isopropylcholesta-5,7-diene* (**5**). To a solution of **2** (0.2 g, 0.49 mmol) in CH_2Cl_2 (5 ml) at -78 °C, was added DAST (0.3 g, 1.8 mmol) in CH_2Cl_2 (5 ml). After 30 min the reaction was treated with MeOH (1 ml), concentrated *in vacuo* and heptane (15 ml) was added. The mixture was washed with 10 ml 5% $NaHCO_3$ and 10 ml H_2O. The organic layer was concentrated and purified by flash chromatography on 50 ml SiO_2 with 5% toluene in heptane as the eluent, giving 30 mg (15%) of **4**: ^1H NMR ($CDCl_3$): δ 6.16 (dd, 2 H, H6, H7), 0.8 and 1.73 (dd, 6 H, H28, H29), 2.6–0.5 (m, 38 H). ^{13}C NMR ($CDCl_3$): δ 147.56 (C14), 135.85 (C3), 132.78 (C4), 125.63 (C6), 123.30 (C8), 122.14 (C7). MS *m/z* (rel. int.): 394 (M^+, 57), 379 (27), 281 (69), 227 (31).

Continued elution gave 80 mg (40%) of **5**: ^1H NMR ($CDCl_3$): δ 5.85 (m, 1 H, H6), 5.5 (m, 1 H, H7), 3.05 (m, 1 H, H4), 1.3 and 1.45 (dd, 6 H, H28, H29), 2.2–0.5 (m, 38 H). ^{13}C NMR ($CDCl_3$): δ 146.95 (C5), 140.52 (C8), 117.49 (C6), 116.73 (C7), 98.5 (d, J_{CF} 165.51 Hz, C3). MS *m/z* (rel. int.): 414.3 (M^+, 60), 379.3 (84), 353.3 (100), 301.2 (42), 281.2 (46), 145.0 (65).

4-Nor-3-isopropylcholesta-3(5),6,8(14)-triene (**6**). Compound **5** (80 mg, 0.2 mmol) in benzene (0.2 ml) and 96% EtOH (2.6 ml) was treated with conc. HCl (0.2 ml). The reaction was refluxed for 2 h, then CH_3CN (1.8 ml) and heptane (5 ml) were added. The organic layer was separated and washed with 5 ml 5% $NaHCO_3$, then 10 ml H_2O and concentrated *in vacuo*. This gave as the only product 50 mg (62.5%), of **6**: ^{1}H NMR ($CDCl_3$): δ 6.12 (q, 1 H), 0.92 and 1.02 (m, H28, H29), 2.9–0.5 (m, 39 H). ^{13}C NMR ($CDCl_3$): δ 147.88 (C14), 140.23 (C3), 138.84 (C5), 125.67 (C8), 124.32 (C6), 118.01 (C7).

5α-Cholesta-8,14-dien-3β-ol (**7**). Compound **1** (2.5 g, 6.5 mmol) was converted into compound **7** by the method previously described,[13] using CH_2Cl_2 instead of CCl_4. The oily yellow product was recrystallized twice from MeOH to yield colourless plates 1.0 g (40%) of **7**: m.p. 100–104.0 °C. ^{1}H NMR ($CDCl_3$): δ 5.37 (s, 1 H, H15), 3.63 (m, 1 H, H3), 2.37 (1 H, H16), 2.36 (1 H, H22), 2.24 (2 H, H11), 2.11 (1 H, H16), 2.07 (1 H, H22), 2.03 (1 H, H12), 1.89 (1 H, H2), 1.86 (1 H, H1), 1.68 (1 H, H4), 1.62 (1 H, H20), 1.56 (1 H, H6), 1.53 (2 H, H5, H25), 1.52 (1 H, H17), 1.49 (1 H, H2), 1.45 (1 H, H6), 1.42 (1 H, H12), 1.38 (2 H, H7, H23), 1.37 (1 H, H4), 1.26 (1 H, H1), 1.17 (1 H, H7), 1.14 (2 H, H24), 1.06 (1 H, H23), 1.00 (3 H, H19), 0.95 (3 H, H21), 0.89 (3 H, H27), 0.87 (3 H, H26), 0.83 (3 H, H18). ^{13}C NMR ($CDCl_3$): δ 151.50 (C14), 141.24 (C9), 123.49 (C8), 117.83 (C15), 71.39 (C3), 57.66 (C17), 45.45 (C13), 41.37 (C5), 39.93 (C24), 38.72 (C4), 37.36 (C12), 36.95 (C10), 36.52 (C22), 36.32 (C23), 35.74 (C1), 34.47 (C20), 32.11 (C2), 28.42 (C25), 27.00 (C16), 25.72 (C6), 24.16 (C7), 23.21 (C26), 22.97 (C27), 21.27 (C11), 19.29 (C21), 18.77 (C19), 16.09 (C18), Anal. Calc. for $C_{27}H_{44}O \cdot 1.07\ H_2O$: C 80.29; H 11.51. Found: C 80.29; H 11.81. MS *m/z* (rel. int.): 384 (M^+, 100), 369 (50), 351 (20), 271 (18). HPLC: (6.70 min) 99.4%.

3α-Fluoro-5α-cholesta-8,14-diene (**8**) *and 5α-cholesta-2,8,14-triene* (**9**). Compound **7** was treated as previously described for androstane derivatives.[14] To a stirred solution of **7** (1.17 g, 3 mmol) in CH_2Cl_2 (10 ml) cooled to −78 °C was added DAST (1.4 g 8.7 mmol) in CH_2Cl_2 (10 ml) over 10 min. After 1.5 h at −78 °C the cooling bath was removed and the reaction warmed to 25 °C. H_2O (15 ml) was added, and after 10 min the organic layer was washed with 30 ml 5% $NaHCO_3$ and 30 ml H_2O. The organic layer was dried over $MgSO_4$, filtered and concentrated. Flash chromatography on 100 ml SiO_2 with heptane as the eluent, gave after recrystallisation from EtOH–MeOH (1:5) 0.23 g (20%) of **9** as colourless crystals: m.p. 104.7 °C (DSC). ^{1}H NMR: δ 5.64 (m, 2 H, H2, H3), 5.35 (s, 1 H, H15), 2.5–0.5 (m, 39 H). ^{13}C NMR: δ 150.91 (C14), 139.45 (C9), 125.96 (C3), 125.67 (C2), 122.98 (C8), 116.91 (C15), MS *m/z* (rel. int.): 366 (M^+, 100), 351 (60), 312 (20), 253 (13). Anal. Calc. for $C_{27}H_{42} \cdot 0.5$ heptane: C 87.91; H 12.09. Found: C 87.91; H 12.10. GC (12.17 min) 100%.

Continued elution with 5% acetone in heptane gave another product, which, after recrystallisation from EtOH–MeOH (1:5), gave 0.14 g (12%) of **8** as colourless translucent crystals: m.p. 98.6 °C (DSC). ^{1}H NMR: δ 5.33 (s, 1 H, H15), 4.81 (d, 1 H, $J_{HF} \approx 48$ Hz, H3–βH) 2.5–0.5 (m, 41 H). ^{13}C NMR: δ 150.71 (C14), 140.22 (C9), 122.64 (C8), 116.85 (C15), 88.61 (d, $J_{CF} = 166$ Hz, C3). ^{19}F NMR: δ −181.12 (tq, $J_{HF} \approx 45$ Hz F3–αF). MS *m/z* (rel. int.): 386.3 (M^+, 90), 371.3 (100), 273.2 (30). Anal. Calc. for $C_{27}H_{43}F$: C 83.88; H 11.21. Found: C 83.92; H 11.75.

5α-Cholesta-8,14-dien-3-one (**10**). Compound **7** (8 g, 20.8 mmol) was converted into **10** as previously described.[15] Chromatography of the oily product on 150 ml SiO_2 with 5% CH_2Cl_2 and 15% diethyl ether in toluene resulted, after recrystallisation from 99% EtOH, in 2.7 g (34%) of **10** as off-white crystals: m.p. 127.8–128.4 °C. ^{1}H NMR: δ 5.38 (s, 1 H, H15), 2.5–0.5 (m, 41 H). ^{13}C NMR: δ 211.02 (C3), 150.22 (C14), 138.55 (C9), 123.36 (C8), 117.87 (C15). MS *m/z* (rel. int.): 382.3 (M^+, 100), 367.3 (65), 269.1 (35), 255.2 (30), 159.1 (30), Anal. Calc. for $C_{27}H_{42}O \cdot 0.19$ EtOH: C84.03; H 11.11. Found: C 84.00; H 11.24. HPLC: (10.29 min) 97.5%.

3,3-Difluoro-5α-cholesta-8,14-diene (**11**). Compound **10** was treated as previously described for androstan derivatives.[14] A glass cylinder equipped with a magnetic stirrer was charged with a solution of **10** (1.0 g, 2.6 mmol) in CH_2Cl_2 (2.5 ml) and a solution of DAST (2.1 g, 12.4 mmol) in CH_2Cl_2 (1 ml) was added. The glass cylinder was sealed and warmed to 50 °C for 4.5 h. The cylinder was cooled to 0 °C, opened and MeOH (5 ml) and heptane (50 ml) added carefully. The mixture was washed twice with 50 ml 5% $NaHCO_3$ and once with 50 ml H_2O and evaporated to dryness, then purified by flash chromatography on 100 ml SiO_2 with 1% EtOAc in heptane as the eluent. Recrystallisation from EtOAc–MeOH (1:5) gave 0.22 g (21%) of **11**: m.p. 95.9 °C (DSC). ^{1}H NMR: δ 5.37 (s, 1 H, H15), 2.5–0.5 (m, 41 H). ^{13}C NMR: δ 150.29 (C14), 138.92 (C9), 123.04 (t, $J_{CF} = 234.7$ Hz, C3), 123.08 (C8), 117.51 (C15). ^{19}F NMR: −90.40 (d, $J_{CF} = 235.6$ Hz), −90.75 (d, $J_{CF} = 234.7$ Hz), −99.04 (dm, $J_{CF} = 234.7$ Hz), −100.86 (dm, $J_{CF} = 232.1$ Hz). MS *m/z* (rel. int.): 404 (M^+, 100), 389 (46), 291 (48), 277 (29). Anal. Calc. for $C_{27}H_{42}F_2$: C 80.15; H 10.46. Found: C 80.07; H 10.80.

5α-Cholesta-8,14-dien-3α-ol (**12**). Compound **10** was treated as previously described for cyclic ketones.[16] To a stirred solution of **10** (1.0 g, 2.6 mmol) in THF (22.1 ml) cooled to −78 °C under N_2 was slowly added 2 ml (1 M, 2 mmol) LS-Selectride®. After 2 min the cooling bath was removed and the mixture allowed to warm to 25 °C. Water (0.4 ml) in 1.5 ml EtOH was added, followed by 4 M NaOH (2 ml) and 30% H_2O_2 (1.5 ml). After stirring for 10 min, 5 ml 5% $NaHCO_3$ were added. The organic

phase was collected and the water phase extracted twice with heptane (5 ml). The three organic phases were combined and dried over $MgSO_4$ and concentrated *in vacuo*. To the resulting white powder were added heptane (75 ml) and H_2O (100 ml), and the mixture stirred for 30 min at 80 °C. The organic phase was separated, dried over $MgSO_4$, and concentrated *in vacuo*. Recrystallisation from MeOH afforded 0.45 g (45%) of **12** as colourless crystals: m.p. 151.3 °C (DSC). ^{1}H NMR: δ 5.33 (s, 1 H, H15), 4.2 (s, 1 H, H3), 2.5–0.5 (m, 41 H). ^{13}C NMR: δ 151.26 (C14), 141.12 (C9), 122.99 (C8), 117.16 (C15), 66.30 (C3). MS *m/z* (rel. int.): 384 (M^+, 100), 369 (46), 351 (42), 271 (15), 238 (22). Anal. Calc. for $C_{27}H_{44}O \cdot 0.15\ H_2O$: C 83.72; H 11.53. Found: C 83.72; H 12.12. HPLC (6.22 min): 98.2%.

3β-Fluoro-5α-cholesta-8,14-diene (**13**) *and 5α-cholesta-2,8,14-triene* (**9**). Compound **12** was treated as previously described for androstan derivatives.[14] To a stirred solution of **12** (0.4 g, 1.04 mmol) in CH_2Cl_2 (10 ml) cooled to −70 °C under N_2 was added cold (−70 °C) DAST (0.17 g, 1.04 mmol) in CH_2Cl_2 (5 ml) over 15 min. After 40 min the mixture was warmed up to 22 °C and MeOH (2 ml) added. The reaction mixture was evaporated to dryness and heptane (10 ml) was added. The organic layer was washed with 10 ml 5% $NaHCO_3$ and 10 ml H_2O, concentrated and purified by flash chromatography on 150 ml SiO_2 with heptane as the eluent. The product was recrystallised from MeOH giving 0.14 g (35%) of **9** as colourless crystals. HPLC (4.83 min): 99.3%.

Continued elution with 5% acetone in heptane followed by recrystallisation from MeOH gave 0.03 g (7.5%) **13** as colourless translucent crystals: m.p. 93.2 °C (DSC). ^{1}H NMR: δ 5.36 (s, 1 H, H15), 4.45 (dm, 1 H, J_{HF} = 49.6 Hz, H3–αH), 2.5–0.5 (m, 41 H). ^{13}C NMR: δ 150.44 (C14), 139.83 (C9), 122.76 (C8), 117.21 (C15), 91.94 (d, J_{CF} = 172.27 Hz; C3). ^{19}F NMR: δ −169.20 (q, intensities 1:5:5:1, J_{HF} = 49.6 Hz, F3–βF). MS *m/z* (rel. int.): 386 (M^+, 100), 371 (80), 273 (33), 259 (26). High-resolution MS: Calc. for $C_{27}H_{43}F$: 386.334 328. Found 386.334 880. HPLC (5.31 min): 99.9%.

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